REMARKS

Introductory remarks

Claims 1-5 and 7-16 were pending before the Office. Claims 2, 9 and 10 are withdrawn from consideration. Claim 6 was previously cancelled. By this Amendment, claims 1, 3-5, 7-8 and 11-16 have been amended. No claims are further cancelled or added. Accordingly, claims 1, 3-5, 7-8 and 11-16 shall be considered on the merits upon entry of this Amendment.

The herein amendments and remarks should in no way be construed as an acquiescence to any of the Examiner's rejections in the Office Action issued in the present application. Applicants reserve the right to pursue the subject matter of the claims as originally filed or similar claims in one or more subsequent applications.

Support for the amendments to the claims can be found throughout the specification, drawings and claims, as originally filed.

No new matter has been added by this response.

Claim Rejections – 35 USC § 103

The Examiner rejected claims 1 and 3-4 under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Publication No. 2005/0071088 to Landfield et al. (herein as "Landfield").

The Examiner further rejected claims 5, 7-8 and 11-16 under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Publication No. 2005/0175626 to Delacourte et al. (herein as "Delacourte") in view of Landfield.

With regard to Landfield, the Office contends that the reference discloses a method of assessing a state of Alzheimer's disease comprising detecting VGF. The Office admits, however, that Landfield does not specifically teach or suggest the recited VGF fragment polypeptide observed and claimed in the method of the invention either in terms of its molecular weight (4824 ±20 Da) as recited in claim 1, or its amino acid sequence (SEQ ID NO: 17) as recited in claims 3-4.

With regard to the combination of Delacourte and Landfield, the Office contends that Delacourte discloses a method of assessing a state of Alzheimer's disease by antibody-based methods that allow for the isolation of specific polypeptides from cerebral spinal fluid samples, followed by the detection of the polypeptides by SELDI-TOF-MS. The Office admits, however,

that Delacourte fails to teach or suggest VGF and turns to the teachings of Landfield to reach the recited invention.

Applicants respectfully disagree and traverse the rejections.

As the Office will appreciate, *Graham v. John Deere Co.,* 338 U.S. 1, 148 USPQ 459 (1966), was reaffirmed by *KSR International Co. v. Teleflex Inc.,* 127 S.Ct. 1727, 82 USPQ2d 1385 (2007) as providing the correct analytical framework for determining obviousness. Under *Graham*, obviousness is a question of law based on underlying factual inquires that address (1) the scope and content of the prior art, (2) the differences between the claimed invention and the prior art, and (3) the level of ordinary skill in the pertinent art. Once these *Graham* factors are resolved, the Examiner must determine whether the claimed invention would have been obvious to one of ordinary skill in the art. M.P.E.P. 2141(III). The Court made clear in *KSR* that such a determination of obviousness must be supported by a "clear articulation of the reason(s) why the claimed invention would have been obvious" and that such reason "supporting a rejection under 35 U.S.C. 103 should be made explicit." *KSR*, 82 USPQ2d at 1396. By doing so, the Office may establish a *prima facie* case of obviousness, which would cause the burden of proof of nonobviousness to shift to the applicants (A) to show that the Office erred in its findings, or (B) provide other evidence to show that the claimed subject matter would have been nonobvious. M.P.E.P. 2141(III).

To establish a *prima facie* case of obviousness, the Office relies on the specific rationale that the combination of references is proper because there exists some teaching, suggestion, or motivation in the prior art that would have led the skilled artisan to modify or combine the cited prior art to arrive at the claimed invention. However, for this rejection to be proper, the prior art references or their combinations must be shown to ***teach or suggest all the claim limitations***. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974). In addition, the rejection requires the Office to articulate (1) a teaching, suggestion or motivation to combine the references and (2) a finding of a reasonable expectation of success. See MPEP § 2143(G).

Applicants respectfully submit that the Office has failed to establish a *prima facie* case of obviousness because that the prior art references, either alone or in combination, do not teach or suggest all of the elements of the claims. Specifically, neither of the cited prior art references teaches or fairly suggests the use of a VGF polypeptide as a biomarker of Alzheimer's disease. Moreover,

given the fact that the cited prior art references fail to teach this critical feature of the invention, the Office has not shown the existence of a reasonable expectation of success that the combination of references would have led to the instantly claimed invention.

In claim 1, the present invention is directed to a method of assessing the state of Alzheimer's disease in a subject comprising detecting a ***specific polypeptide fragment of VGF*** having a molecular mass of 4824 ±20 Da wherein the molecular mass is observable by SELDI-TOF-MS using a strong anion exchange array. In claims 3 and 4, the present invention is also directed to a method of assessing the state of Alzheimer's disease in a subject comprising detecting a polypeptide of SEQ ID NO: 17, or at least 5 contiguous amino acids of the polypeptide of SEQ ID NO: 17. Table 1 and Example 10 of the specification show that SEQ ID NO: 17 is a 20-amino acid polypeptide fragment of VGF having a SELDI-observed molecular weight of 4823.5 ±1.7 Da. Each of the remaining claims depend from claims 1, 3 or 4. Thus, each of the claims of the present invention are directed to methods that require specific polypeptide fragments of VGF as biomarkers of Alzheimer's disease.

Neither Landfield nor Delacourte teach or suggest the specifically claimed polypeptide biomarkers; and thus, neither reference, either alone or in combination, renders the claims obvious.

Landfield discloses a general "strategy" for identifying numerous biomarkers that may be useful for assessing "aging-related cognitive impairment." Although Landfield's group of biomarkers includes VGF (see, e.g., Table 1), Landfield does not teach or suggest or exemplify that VGF has any link to Alzheimer's disease as a biomarker. In fact, Landfield fails to teach or exemplify any one specific biomarker specifically useful in evaluating Alzheimer's disease. Moreover, Landfield fails to disclose or recognize even a single polypeptide fragment of VGF, nor does it teach or suggest or exemplify that any such VGF polypeptide—were they disclosed at all—could have any particular use as a biomarker of Alzheimer's disease. Instead, Landfield lists VGF as one of many identified biomarkers generally for "aging-related cognitive impairment" and does not specifically link VGF—or any polypeptide fragments of VGF—as a biomarker of Alzheimer's disease. Indeed, Landfield contains no disclosure whatsoever regarding the specifically claimed VGF polypeptides, nor their particular link as useful biomarkers of Alzheimer's disease. Specifically, no where does Landfield teach, suggest or exemplify the ***specifically claimed polypeptide fragments of***

VGF having the specified molecular mass of 4824 ±20 Da or the amino acid sequence of SEQ ID NO: 17. Landfield further does not provide any teachings or guidance or direction as to the existence of such polypeptide fragments or how one might identify such fragments, or that even if identified, whether such fragments would have any specific link whatsoever to Alzheimer's disease.

One of ordinary skill in the art will appreciate that the VGF gene encodes a precursor polypeptide of 615 amino acids, which is then proteolytically processed into multiple different mature peptides of various masses each of which have a variety of functions. See Specification, page 7, lines 14-22 and Thakker-Varia et al., "Neuropeptides in depression: role of VGF," *Behav Brain Res.* 2009, Feb. 11; 197(2): 262-278. The present invention is based, in part, on the surprising discovery that "specific polypeptides are differentially expressed in subjects having Alzheimer's disease when compared to a healthy control group. These differentially expressed polypeptides can be, e.g., detected in samples of cerebrospinal fluid of the subject in which Alzheimer's disease is to be diagnosed." See Specification, page 5, lines 26-31. As such, the claims require ***specific*** polypeptides of VGF as defined by a specific molecular mass (claim 1) or an amino acid sequence (claims 3 and 4) that have been surprisingly found to be of particular use in assessing the state of Alzheimer's disease in a subject. To the contrary, Landfield makes no specific link between VGF and Alzheimer's disease, nor does it expressly recognize specific polypeptides of VGF—including those polypeptides having a molecular mass of 4824 ±20 Da or the amino acid sequence of SEQ ID NO: 17—that have any particularly link as indicators of Alzheimer's disease.

Delacourte does not cure the deficiencies of Landfield, nor does it alone teach or suggest all of the elements of the claimed invention. The Examiner contends that Delacourte discloses a method of assessing a state of Alzheimer's disease comprising separating polypeptides from cerebral spinal fluid using antibodies specific to those polypeptides, followed by their detection using SELDI-TOF-MS. The Examiner, however, admits that Delacourte fails to disclose VGF as a biomarker for Alzheimer's. Instead, Delacourte is concerned only with β-amyloid polypeptides—of which VGF is not a member. The Examiner turns to Landfield's minimal disclosure of VGF to reach the present invention. Applicants respectfully submit, however, that this combination of references does not establish a *prima facie* case of obviousness because neither of the references contains any teachings

as to the specific VGF polypeptides recited in and required by the claims, i.e., those polypeptides having a molecular mass of 4824 ±20 Da or the amino acid sequence of SEQ ID NO: 17.

Accordingly, even if the references were properly combinable, which is not admitted here, the combination of Landfield and Delacourt do not teach or fairly suggest all of the recited elements of the invention; and thus, cannot render the claims obvious.

Moreover, because neither reference provides any guidance or teachings regarding VGF-derived polypeptides, or any guidance as to which VGF-derived polypeptides would have been linked to Alzheimer's disease, one of ordinary skill in the art would not have had any reasonable expectation of success in carrying out the claimed invention in view of the combination of references. Specifically, the skilled person would not have expected to be able to carry out a method of assessing a state of Alzheimer's disease that relies on the detection of specific polypeptide fragments of VGF in view of references which do not teach or suggest or even recognize the claimed polypeptides or their particular usefulness as biomarkers of Alzheimer's disease.

In view of the above, Applicants respectfully assert that none of the cited references, either alone or in any combination, teach or suggest all of the elements of the claimed invention. Thus, a *prima facie* case of obviousness has not been established. Even if a *prima facie* case of obviousness were properly made, which is not admitted here, the skilled artisan would not have had a reasonable expectation of success that the instantly claimed invention could have been achieved.

Applicants respectfully request reconsideration and withdrawal of the Section 103 rejections.

CONCLUSION

In view of the remarks made herein, the application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are respectfully requested. Please charge any required fee or credit any overpayment to Deposit Account No. 04-1105, reference number LeA36293[83672(303989)].

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